Declaration

In the United States Patent Office

In re Application of

Karin Klokkers, Kai-Thomas Kramer, Wilfried Fischer and Anna Sendl-Lang

Application No.: 10/019 121

International filing date: July 12, 2001

Title: Matrix-controlled transdermal system for stable derivatives of ACE inhibitors

1. I, Joerg Nink, of Industriestrasse 25, D-83607 Holzkirchen, Germany, am a senior scientist for TTS development at Hexal AG to which the application identified above has been assigned. I hold a degree as a chemical engineer from Darmstadt University, Germany.

I am the same Joerg Nink who previously made a Declaration in these proceedings dated May 29, 2007.

I understand that some scepticism has been expressed about the significance of the experimental data provided in my previous Declaration. I now wish to clarify certain points and, especially, address Examiner's remarks at page 7 of the Office

Action dated April 01, 2008 by providing a "proper comparison" of equivalent compositions.

2. The tested ACE inhibitors are the state of the art prodrug trandolapril (monoester) and the stabilized diester derivative trandolaprilethylester according to the present invention. All other parameters are equivalent. In particular, when testing said two ACE inhibitors in transdermal therapeutic systems it was observed that:

(i) the drugs employed had the same purity;

(ii) the concentration of the drugs in the TTS was the same;

(iii) the same adhesive was used; and

(iv) the same storage conditions were applied throughout.

2.1. The improved stability of the claimed composition is readily apparent from the results of my stability tests, which are shown in Table 1 below.

TABLE 1

ACE inhibitor	Matrix components [%]	Purity of drug employed	Purity after storage			Permeation [µg/cm²h]
			14 days	+4weeks (PS)	+4weeks (AS)	
Trandolapril (monoester)	5% ACE inhibitor 95% acrylat (87-4287)	99%	71%	37%	6%	-*
Trandolapril (monoester)	10% ACE inhibitor 90% acrylat (87-4287)	99%	75%	49%	41%	-*
trandolapril ethylester (diester)	5% ACE inhibitor 95% acrylat (87-4287)	99%	99%	99%	97%	0,7
trandolapril ethylester (diester)	10% ACE inhibitor 90% acrylat (87-4287)	99%	99%	99%	98%	1,2

*: due to the rapid decline of the drug in the transdermal therapeutic system, it was not possible to determine a correct permeation rate in comparison to a transdermal therapeutic system where an equally concentrated diester-drug was employed.
PS: permanent stability 25°C/60°humidity
AS: accelerate stability 40°C/75°humidity

2.2. The above results of the comparison of the stability of the monoester and diester form of trandolapril in a matrix-controlled transdermal therapeutic system clearly demonstrate that the diester form is by far more stable than the prior art monoester compound. In fact, it was observed that more than 50% of the monoester drug decomposed during storage. In contrast, almost no degradation of the diester compound was observed.

3. I further declare, that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of the U.S. code, and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 21.08.2008 Signature: .....